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CLINICAL INVESTIGATION

Idiopathic hypercalciuria associated with hyperreninemia and high urinary prostaglandin E

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Idiopathic hypercalciuria associated with hyperreninemia and high urinary prostaglandin E. A patient with idiopathic hypercalciuria and some features suggestive of Bartter syndrome is reported. Excessive urinary prostaglandin E (PGE) excretion and renal calcium leak were documented in this child. Treatment with aspirin and indomethacin reduced urinary PGE excretion and was associated with a decrease in daily calcium excretion. At the lowest levels of urinary PGE, the renal calcium leak was no longer evident although mild hypercalciuria persisted. These results suggest that PGE may play a role in some cases of idiopathic hypercalciuria.

Hypercalciurie idiopathique associée à une hyperréninémie et à des prostaglandines E urinaires élevées. On rapporte un malade porteur d'une hypercalciurie idiopathique et de quelques caractéristiques suggérant un syndrome de Bartter. Une excrétion excessive de prostaglandines E (PGE) urinaires et une fuite rénale calcique ont été documentées chez cet enfant. Un traîtement par de l'aspirine et de l'indométhacine a réduit l'excrétion urinaire de PGE et s'est accompagné d'une diminution de l'excrétion calcique journalière. Pour les plus faibles niveaux de PGE urinaires, la fuite rénale calcique n'était plus évidente bien que persiste une hypercalciurie modérée. Ces résultats suggèrent que les PGE pourraient jouer un rôle dans certains cas d'hypercalciurie idiopathique.

Idiopathic hypercalciuria is a common occurrence in the healthy adult population [1] and is found in 40 to 60% of patients with recurrent calcium nephrolithiasis [1–3]. The disorder appears to have a genetic basis [1] and is thought to have a similar prevalence in children [4]. The pathogenesis of hypercalciuria is still controversial [2, 5–7] although two major mechanisms emerge [8]. Some patients have a primary defect of intestinal hyperabsorption of calcium [8–9], while in others, the defect is felt to be an impairment of renal tubular calcium reabsorption [6, 8, 9]. Renal phosphate wasting has been identified in some patients and suggested as an etiologic factor in idiopathic hypercalciuria [2, 7, 10, 11], although some authors consider it to be simply a subset [12]. Recent evidence also suggests a proximal tubular defect in salt and water reabsorption [2, 13] which has been offered as a cause of phosphate wasting and hypercalciuria [2].

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In children, idiopathic hypercalciuria has been less well characterized but seems to occur in a sizable percentage of healthy children and may be associated with a variety of urinary tract symptoms [4, 14]. Stapleton et al [15] studied a group of 21 children with calcium urolithiasis using oral calcium-loading studies and found that 80% had idiopathic hypercalciuria. Of these patients, 82% had renal hypercalciuria and 18% had absorptive hypercalciuria. The presence of phosphate wasting with absorptive hypercalciuria has also been reported in children [16]. Urolithiasis, however, is not the only abnormality associated with idiopathic hypercalciuria in children [14, 17]. Royer et al [17] reported ten children with hypercalciuria associated with nephrocalcinosis, growth failure, polydipsia, polyuria, defective renal concentrating capacity, and osteoporosis. Subsequently, other children with hypercalciuria and nephrocalcinosis or rickets have been reported [14, 18–21]. Many of the latter have had features suggestive of Bartter syndrome associated with multiple tubular defects [18–22].

We describe a patient with idiopathic hypercalciuria associated with polyuria, polydipsia, hyperreninemia, and nephrocalcinosis. A detailed metabolic evaluation of this child suggested the presence of a prostaglandin-mediated defect in renal tubular calcium reabsorption.

Case report

This patient exhibited symptoms at 19 months of age when his mother noted excessive thirst. Fluid intake was approximately 2 liters/day; a random urinalysis was normal (specific gravity: 1.004). When 4 years old the patient was recognized to have growth failure, polydipsia now approaching 4 liters each day, and enuresis. Urine osmolality was 365 mOsm/kg H_2O after dehydration and the administration of 5 U of aqueous vasopressin. Nephrocalcinosis was subsequently demonstrated without evidence of primary hyperparathyroidism, vitamin D intoxication, renal tubular acidosis, hyperoxaluria, or Fanconi syndrome. Twenty-four-hour urinary calcium excretion was 9.6 mg/kg (normal < 4 mg/kg) and was unchanged following 12 hr of fasting. A diagnosis of idiopathic renal hypercalciuria was made, and the patient was started on a thiazide diuretic in addition to a diet low in calcium and sodium. Calcium excretion tended to decrease on this regimen but was variable (6.6 to 10.5 mg/kg). In addition, this therapy was associated with hypokalemia (2.3 to 3.0 mEq/liter) despite oral

potassium chloride supplementation of up to 120 mEq/day (7.5 mEq/kg). Because of the ineffectiveness of the thiazide therapy and its associated hypokalemia, the diuretic and potassium chloride supplementation was discontinued. Subsequently, urine calcium increased (20 to 22 mg/kg/day) as did urine volume (2250 to 3000 cc/day) and serum potassium (3.2 to 3.9 mEq/liter).

At 6 years of age, the child was evaluated further to better characterize the hypercalciuria. A modified protocol based on the studies of Pak et al [9] was utilized. Following stabilization on a low calcium diet, fasting calcium excretion was 0.7 mg/mg creatinine (normal in children < 0.2); parathormone (PTH) was 120 μlEq/ml (Nichols Institute, Los Angeles, California; normal < 100) and urinary cyclic AMP was 18.1 μmoles/g creatinine (normal < 7). After a 500-mg calcium meal, calcium excretion increased to 0.92 mg/mg creatinine (normal in children < 0.27) and urinary cyclic AMP decreased to 12.6 μmoles/g creatinine. In addition, the child had an elevated supine plasma renin activity (PRA) (46 ng angiotensin I/ml/hr; normal < 5.5), urinary aldosterone excretion (21 μg/day; normal < 15), and insensitivity to the pressor effects of angiotensin II, requiring 60 μg/kg/min for a 20-mm increase in diastolic BP. A blood volume determination and a renal biopsy were normal; there was no evidence of juxtaglomerular cell hyperplasia. The patient was considered to be a variant of Bartter syndrome demonstrating idiopathic renal hypercalciuria and nephrocalcinosis [19, 20, 22].

A trial of salicylate therapy was begun. The polyuria decreased, enuresis disappeared, and PRA returned to normal. These findings were associated with a decrease in urinary calcium excretion. When salicylates were discontinued, the symptoms of polyuria recurred along with the hypercalciuria. Based on this experience, a protocol was designed to assess the effects of prostaglandin inhibition using aspirin and indomethacin, two chemically dissimilar inhibitors of cyclo-oxygenase [23].

Methods

To initiate the study, all previous therapy as well as diet restrictions were withdrawn. Two weeks later, duplicate 24-hr urine collections were obtained at home; these samples were designated as baseline. The child was then placed on a diet consisting of 1900 calories, 400 mg calcium, 800 mg phosphorus, 80 mEq sodium, 60 mEq potassium, 75 g protein, and ad lib fluid intake; compliance was monitored at home using a diet diary. Following a 2-week period of stabilization on this diet, the study protocol was initiated. This protocol consisted of four identical 6-day evaluations in the clinical research center at the University of Minnesota Hospitals. The first study (designated diet modified or period 1) was done while the child was not receiving therapy. The second and third studies, designated periods 2 and 3, were done while the child received 60 and 100 mg/kg of aspirin and the fourth during therapy with 3 mg/kg of indomethacin (period 4). Each evaluation was separated by at least 2 weeks to allow for adequate stabilization on drug therapy.

During each of the four study periods, the following sequence of investigation was used. The day 1 allowed for acclimatization to the Clinical Research Center as well as monitoring of dietary intake. On days 2 and 3, 24-hr urine collections and blood samples were obtained. All of the 24-hr samples were analyzed for electrolytes, creatinine, calcium, phosphorus, magnesium, citrate, oxalate, uric acid, PGE, and urinary saturation kinetics were done. The blood samples were analyzed for electrolytes, bicarbonate, creatinine, ionized calcium, phosphorus, 25-hydroxyvitamin D (25-OHD), 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$] as well as supine and 2-hr upright PRA.

The maximal urinary concentrating capacity was assessed on day 4 [24] of each study period. With no preceding fluid restriction, the child was given 20 μg of DDAVP intranasally. One hour later, he was instructed to empty his bladder by double voiding; subsequently, two 2-hr urine collections were obtained for osmolality. The correlation between maximal urine osmolality obtained by this method as compared to prolonged dehydration or dehydration and pitressin is excellent [24]. Following this study and the evening meal, the patient was fasted but allowed free access to distilled water. The following morning (day 5), an oral calcium-loading study was performed [9, 25]. The protocol utilized was identical to that described by Pak et al [9], except that the oral calcium load consisted of 250 calories, 650 mg calcium, 15 mEq sodium, and 75 mg phosphorus. On day 6, tubular function was evaluated during maximal free-water diuresis using accepted clearance methods [26, 27]. To suppress endogenous vasopressin, an oral load of 900 ml (30 ml/kg) of water was given over 1 hr followed by 20 ml/kg/hr. When urine volume was stable at a value greater than 8 ml/min, two 1-hr urine collections were obtained along with midpoint blood samples.

Four age-matched normal children were used as control subjects for baseline urinary excretion data only. These children were not subjected to diet modification or therapy prior to obtaining a single 24-hr urine collection for the assessment of PGE, calcium, and sodium excretion. This study was approved by the committee on the use of Human Subjects in Research at the University of Minnesota and informed written consent was obtained.

Routine blood and urine chemistries were analyzed according to standard techniques in the University of Minnesota Hospital Clinical Laboratory. Ionized calcium (normal 4.4 to 4.8 mg/dl) was measured by an ion selective electrode (Orion®, Cambridge, Massachusetts). Oxalate determinations were done using the technique of Hodgkinson and Williams [28]; urinary citrate was measured using the citrate lyase method [29]. Urinary cyclic AMP (normal < 7 μmoles/g creatinine), PTH (Nichols Institute; normal < 100 μlEq/ml), PRA (normal < 5.5 ng angiotensin I/ml/hr [supine]; < 7.8 [upright]) and PGE were all measured by radioimmunoassay using standard techniques [30–33]. 1,25 $(OH)_2D$ (adult normal, 16 to 46 pg/ml; children's normals, 11 to 111 pg/ml [34]) and 25-OHD (normal 20 to 90 ng/ml) were measured using competitive binding assays, according to the methods of Mallon et al (Roche Clinical Labs., Raritan, New Jersey) [35] and Belsey, DeLuca, and Potts [36].

The concentration product ratios and formation product ratios for brushite and calcium oxalate monohydrate were calculated using a modification of the technique of Pak, Ohata, and Holt [37] and Pak et al [38]. Tubular reabsorption of phosphate (TRP) was calculated using the standard formula and the renal threshold phosphate concentration ($TMPO_4$/GFR) was derived using the nomogram of Walton and Bijvoet [39].

Table 1. Baseline daily urinary excretion in the patient and four normal children

	Normal children					
	A	B	C	D	(mean ± SD)	Patient
Volume, *ml/kg*	23.1	28.9	21.7	43.6	(29.3 ± 10.0)	112.5[a]
Calcium, *mg/kg*	1.1	2.4	1.8	1.8	(1.8 ± 0.5)	17.2[a]
PGE, *ng/kg*	6.4	5.6	4.4	5.8	(5.6 ± 0.8)	24.9[a]
Sodium, *mEq/kg*	1.9	3.5	2.6	5.5	(3.4 ± 1.6)	5.8

[a] A value outside the 99% confidence limits was established for normal subjects.

Statistical comparisons between urinary excretion in the controls and the patient were done by establishing confidence limits for each parameter in the normal children. Comparisons between Baseline and study periods 1 through 4 were done using one-way analysis of variance followed by Newman-Keuls multiple comparisons [40]. Linear regressions were calculated using the least squares method.

Results

Baseline daily urinary excretion in this patient and four normal children on a free choice diet is shown in Table 1. When compared with normal children, the patient had a tenfold increase in calcium excretion along with a fourfold increase in urine volume and PGE excretion. Sodium excretion, although higher in the patient, was not significntly different from control subjects.

Table 2 details daily urinary excretion as well as renal function on days 2 and 3 during each study. In response to diet modification (period 1), the patient demonstrated a significant reduction in urinary sodium, chloride, phosphorus and calcium ($P < 0.05$) although absolute calcium excretion was still elevated. Coincident with these changes, urine volume decreased ($P > 0.1$) and PGE excretion rose ($P < 0.05$). Citrate excretion which had been in the low normal range [41] during baseline increased significantly ($P < 0.05$); there was no further change in citrate, sodium, chloride, or phosphorus excretion during the remainder of the study. Potassium, magnesium, uric acid, and oxalate excretion were all normal at baseline (data not shown) and were unchanged during the other periods. During low-dose aspirin therapy (period 2), the salicylate level was 16 mg/dl; there was a moderate reduction in urine volume ($P > 0.1$) as well as a significant reduction in PGE and calcium excretion ($P < 0.05$). Increasing the aspirin dose to 100 mg/kg produced a salicylate level of 31 mg/dl without signs of salicylate intoxication (period 3). As shown, this was associated with a further reduction in urine volume, calcium, and PGE excretion. Urine volume and PGE excretion were reduced as compared to period 1 ($P < 0.05$), although the changes were not significant between periods 2 and 3. Calcium excretion, however, was reduced by increasing the dose of aspirin ($P < 0.05$). There was a further reduction in urine volume and PGE excretion with near normalization of daily urinary calcium excretion following treatment with indomethacin (period 4). Positive correlations were found between urine volume, calcium, and PGE excretion during periods 1 through 4. The correlation coefficients between PGE and calcium excretion ($r = 0.84$; $P < 0.01$), PGE excretion and urine volume ($r = 0.93$; $P < 0.001$) as well as calcium excretion and urine volume ($r = 0.98$; $P < 0.001$) were all significant.

Serum chemistries were normal during periods 1 to 4 except for a mild depression of ionized calcium during periods 1 (4.3 mg/dl) and 4 (4.2 mg/dl). There was a slight increase in 25 OHD that was present throughout the study. It is important to note that there was no significant ($P > 0.3$) change in GFR (Table 2) or in the filtered load of calcium during the treatment periods which might explain the reduction in calcium excretion.

Figure 1 depicts supine and upright PRA contrasted with daily urinary PGE excretion during periods 1 through 4. Supine and upright PRA and PGE excretion were elevated in period 1 and were markedly reduced during the treatment periods. The correlation between PRA and PGE excretion was nearly perfect (PGE and supine PRA, $r = 0.986$, $P < 0.02$; PGE and upright PRA, $r = 0.997$, $P < 0.01$).

Maximum urinary concentrating capacity after DDAVP administration is shown in relation to daily urine volume and PGE excretion in each of the four periods in Table 3. Urine volume and PGE excretion decreased during the study associated with aspirin and indomethacin therapy. Coincident with this, maximum concentrating capacity increased although not into the normal range. Inverse correlations were found between PGE excretion and maximal concentrating capacity ($r = -0.87$; $P < 0.01$) and between daily urine volume and maximum concentrating capacity ($r = -0.995$; $P < 0.01$).

Table 4 provides the data obtained during the calcium-loading study in each period. Fasting urinary calcium/creatinine ratios were high during periods 1 and 2 and were normalized during the high-dose aspirin and indomethacin periods. Following the calcium meal, calcium excretion was high in periods 1 and 2 but fell to normal levels in periods 3 and 4 [25]. PTH was elevated in period 1 but not during therapy. Fasting urinary cyclic AMP values were normal and decreased after calcium loading in all periods. Urinary cyclic AMP did not correlate with circulating PTH levels ($r = -0.04$). TRP varied from 93 to 99% and $TMPO_4$/GFR ranged from 5.4 to 7.4 mg/dl during the study (data not shown); all of these values are normal [42].

The results obtained during maximal free-water clearance are given in Table 5. During period 1, the patient was able to produce a maximally dilute urine (41 mOsm/kg). Distal chloride delivery ($C_{Cl} + C_{H_2O}$), reflecting proximal tubular function, was normal as was distal tubular function estimated from the distal fractional reabsorption of chloride ($C_{H_2O}/C_{H_2O} + C_{Cl}$) [26, 27]. These findings are not consistent with the generally recognized defect in chloride reabsorption seen in Bartter syndrome [20, 22, 26, 27]. Tubular function and GFR were not appreciably changed by either aspirin or indomethacin.

Urinary saturation kinetics were measured during each period and demonstrated that at baseline, the patient's urine was mildly supersaturated with calcium oxalate and brushite. During the study, as both calcium excretion and urine volume decreased, the urine became more supersaturated with calcium oxalate while brushite saturation was not appreciably altered. The formation product ratios, which reflect the limit of metastability, were normal during baseline and decreased slightly during the study but not to abnormal values [43].

Table 2. Renal function and daily urinary excretion[a]

		Study period			
	Baseline	1 Diet modified	2 Low-dose aspirin	3 High-dose aspirin	4 Indomethacin
Volume, *ml/kg*	112.5	90.3	63.5	50.7[b]	42[b]
Calcium, *mg/kg*	17.2	10.5	8.1[b]	5.1[c]	4.1[c]
Prostaglandin E, *ng/kg*	24.9	71.3	6.7[b]	4.1[b]	2.8[b]
Sodium, *mEq*	174	82	74	77	76
Chloride, *mEq*	144	61	64	65	67
Phosphorus, *mg*	994	515	672	653	494
Citrate, *mmoles*	0.48	1.49	1.96	1.92	1.8
Creatinine clearance, *ml/min/1.73 m²*	ND	108	108	106	101

Abbreviation: ND, creatinine clearance not done during Baseline; clearance values are not different during periods 1 to 4.
[a] All values except urine volume during period 1 are significantly ($P < 0.05$) different from Baseline.
[b] $P < 0.05$ compared to Baseline and Diet modified.
[c] $P < 0.05$ compared to Baseline, Diet modified, and Low-dose aspirin.

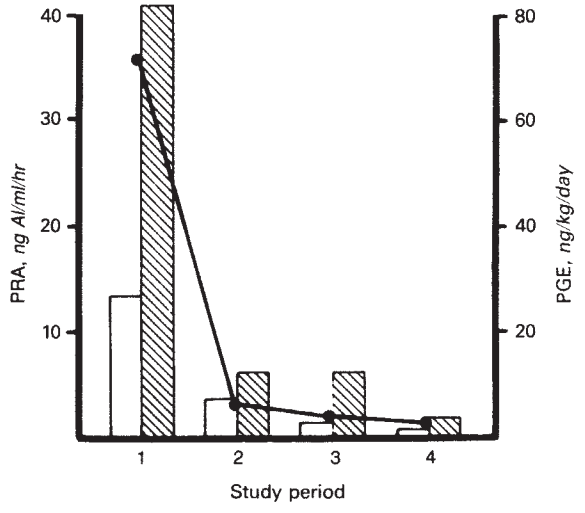

Fig. 1. *Comparison of supine (□) and upright (□) plasma renin activity (PRA) with daily prostaglandin E (PGE, ●—●) excretion while diet modified (period 1) or following treatment with aspirin (periods 2 and 3) or indomethacin (period 4).* PRA in children (mean ± SD) is 2.7 ± 1.4 ng AI/ml/hr (supine) and 4.0 ± 1.9 (upright). AI represents angiotension I.

Discussion

The patient we report has idiopathic hypercalciuria, defined by calcium excretion greater than 4 mg/kg/day on a normal calcium diet in the absence of hypercalcemia or other recognizable causes of hypercalciuria [6, 7, 14]. In addition, this child was documented to have many features suggestive of Bartter syndrome, that is, growth failure in infancy, polyuria, elevated PRA and aldosterone excretion, insensitivity to the effects of angiotensin II, and increased amounts of urinary PGE [20, 22, 26]. He did not, however, demonstrate spontaneous potassium wasting with hypokalemia, alkalosis, or a defect in proximal or distal tubular sodium or chloride handling (Table 4) usually seen in these patients [20, 22, 26, 27]. Similar patients with hypercalciuria associated with Bartter-like syndromes have been reported [17–21], although these patients generally had hypokalemia and features suggestive of renal tubular acidosis or Fanconi syndrome which were not present in our patient.

The initial calcium-loading studies (Table 4) performed during period 1 when the patient was on a restricted diet demonstrated renal leak hypercalciuria as defined by Pak et al in adults [3, 9] and by Stapleton et al in children [25]. It is of interest that in the face of an elevated PTH, normal serum phosphorus and decreased ionized calcium, that the level of 1,25-OH_2D was not strikingly elevated [34, 44, 45] and that the TRP, $TMPO_4$/GFR and urinary cyclic AMP were normal. The latter findings may be secondary to the excessive PGE excretion, since Dominquez et al [46] has shown that PGE_2 infusions inhibit PTH-sensitive adenylate cyclase and phosphaturia in the dog. Following treatment with low-dose aspirin (period 2), the patient had a significant decrease in daily PGE excretion (Table 2) into a range comparable to the normal children. In addition there was a reduction in daily calcium excretion, although not into the normal range [6, 7, 14]. The "renal calcium leak" improved and was associated with the normalization of ionized calcium and PTH as well as a reduction in 1,25,OH_2D. During periods 3 and 4, fasting hypercalciuria was not present, suggesting that the renal tubular defect in calcium excretion had been corrected following therapy with high-dose aspirin and indomethacin. Urinary calcium excretion following calcium-loading studies in periods 3 and 4 (Table 4) approached normal, demonstrating a marked reduction in the absorptive component of the hypercalciuria. Since the patients of Stapleton et al [25] were placed on a more restricted calcium diet, we are not able to determine if calcium excretion is elevated following the calcium meal in these periods; the persistence of elevated daily calcium excretion with normal fasting excretion suggests that a mild absorptive component persists. It must be acknowledged that 25-OHD levels were slightly elevated in all periods. This study was done during the summer and early fall when 25-OHD levels are highest [47]. We would not expect gastrointestinal calcium absorption to be augmented by levels in this range [44, 45].

Although recent reports have suggested the presence of a proximal tubular defect in salt and water handling in some patients with idiopathic hypercalciuria [2, 13], we did not identify such a defect in our patient or document any change in tubular function following therapy (Table 5). Furthermore, our

Table 3. Concentrating capacity, urine volume and prostaglandin E excretion

	Study period			
	1 Diet modified	2 Low-dose aspirin	3 High-dose aspirin	4 Indomethacin
Urine volume, *ml/kg/day*	90.3	63.5	50.7	42
Prostaglandin E excretion, *ng/kg/day*	71.3	6.7	4.1	2.8
Maximum concentrating capacity, *mOsm/kg H_2O*	325	400	447	486

Table 4. Parathormone, urinary calcium and cyclic AMP during fasting and calcium loading

		Study period			
		1 Diet modified	2 Low-dose aspirin	3 High-dose aspirin	4 Indomethacin
Urinary calcium/creatinine, *mg/mg*	FAST	0.46	0.37	0.13	0.07
	LOAD	0.88	0.47	0.22	0.27
Parathormone, *μlEq/ml*	FAST	141	79	78	ND
	LOAD	119	88	74	81
Urinary cAMP, *μmoles/g cr*	FAST	4.6	5.9	4.9	5.1
	LOAD	4.1	5.2	3.3	3.9

Abbreviation: ND, Not done; cr, creatinine.

Table 5. Studies during maximal free-water clearance

	Study period			
	1 Diet modified	2 Low-dose aspirin	3 High-dose aspirin	4 Indomethacin
S_{Osm}	267	269	275	269
U_{Osm}	41	65	70	67
V[a]	10.0	12.5	11.0	11.0
C_{H_2O}[a]	8.5	9.5	8.2	8.3
C_{Osm}[a]	1.5	3.0	2.8	2.7
C_{Cl}[a]	1.2	2.0	1.5	1.4
DD_{Cl}[a]	9.7	11.4	9.6	9.7
DR_{Cl}	0.88	0.83	0.84	0.85
C_{Cr}	116	112	106	120

Abbreviations: S_{Osm}, serum osmolality; U_{Osm}, urine osmolality; V, urine flow; C_{H_2O}, free water clearance; C_{Osm}, osmolar clearance; C_{Cl}, chloride clearance; DD_{Cl}, distal delivery of chloride; DR_{Cl}, distal fractional reabsorption of chloride; C_{Cr}, creatinine clearance (ml/min/1.73 m^2).

[a] The unit of measure used was ml/min/dl glomerular filtrate.

patient had a normal TRP, $TMPO_4$/GFR and serum phosphorus which demonstrates that renal phosphorus wasting is not present [2, 7, 10–12].

Therapy in any type of stone disease is usually directed to decreasing the state of saturation of the urine for stone-forming elements. Correcting the hypercalciuria in this patient was associated with increasing saturation of the urine for calcium oxalate. Because there was no increase in oxalate excretion, this can best be explained by the simultaneous fall in urine volume. Therapy in this child would best consist of prostaglandin inhibition and a high fluid intake.

We are uncertain about the primary stimulus for the excessive PGE excretion seen in our patient. Although there are a large number of recognized mediators of renal PGE synthesis [48], none seem immediately applicable in our patient. Severe dietary sodium restriction leading to volume contraction is a potent stimulus to renin release and PGE synthesis [49, 50]. The level of dietary sodium in our patient, even during periods 1 to 4, would be unlikely to induce sodium depletion, especially in the absence of any abnormality in renal tubular sodium handling. In fact, dietary sodium was likely higher in our patient than in the normal children when his urinary PGE excretion was significantly higher (Table 1). It has also been suggested recently that polyuria may result in increased urinary PGE excretion [51]. However, in this patient, urinary PGE excretion increased (period 1) following dietary modification while the urine volume decreased. This suggests that polyuria was not an independent variable affecting PGE excretion.

While the mechanism leading to excessive PGE synthesis is unclear, we feel that it is likely responsible for the elevation in PRA and partially responsible for the polyuria and concentrating defect seen in this child [50, 52, 53]. As mentioned previously, we do not feel volume contraction played a role in the elevated PRA. It is possible that the elevation in PRA is a primary event or that it might be associated with the abnormality in calcium handling [54, 55]. However, as prostaglandins stimulate renin release [53], it is more likely that the high PRA is secondary to the increased synthesis of PGE. The significant correlation between PGE exretion and PRA ($r = 0.99$) would support this contention.

The most clinically impressive effect of aspirin or indomethacin on this patient was the improvement in polydipsia and loss of enuresis following initiation of therapy. Although the patient has nephrocalcinosis and thus is not able to achieve maximal urinary concentration, we were able to improve the concentrating defect following therapy with either aspirin or indomethacin. A significant correlation was found between PGE excretion and daily urine volume as well as maximum concentrating capacity induced by DDAVP (Table 3). PGE has long been recognized to influence renal water excretion, both by inhibiting arginine vasopressin induced hydro-osmotic water flow and lowering renal medullary interstitial osmolality [50, 52, 56]. Previous in vivo studies in both humans and animals have documented this improvement in vasopressin-induced maximum

concentrating capacity following prostaglandin synthesis inhibition [56]. Although it is possible that the improvement in urinary concentrating capacity may be related to the decrease in renal calcium excretion [57], we feel that it is more likely due to a decrease in urinary PGE.

Our report is the first to document improvement in idiopathic hypercalciuria following treatment with indomethacin. The previous reports noting improvement in hypercalciuria following indomethacin have occurred in patients with renal tubular acidosis or Bartter syndrome [19, 21, 58, 59]. In addition, the elevated urinary PGE excretion suggests a role for prostaglandins in mediating the "renal leak" seen in this patient. However, several points must be made concerning the use of nonsteroidal agents and assumptions concerning prostaglandin mechanisms. These agents are not selective inhibitors of cyclooxygenase and have multiple metabolic effects not associated with prostaglandin metabolism [23, 60]. By using chemically dissimilar agents in differing dosages, we have been able to show a positive correlation between urinary PGE and calcium excretion. This suggests that the correlation is between PGE and calcium excretion and not some nonspecific effect of the nonsteroidal agents. As we did not measure other prostaglandins, it is conceivable that another metabolite might be implicated, although we feel that PGE is the most likely candidate [48, 50, 60]. PGE is recognized to have an effect on sodium transport [50] and has been shown to increase sodium and calcium excretion in the dog [61, 62]. Berl [63] has presented data suggesting that prostaglandins, likely PGE [50, 52], inhibit the hydro-osmotic effect of vasopressin by impairing cellular calcium transport, a finding which may have relevance to the hypercalciuria and polyuria seen in this patient.

Urinary calcium excretion in humans is influenced by many factors, most of which are dietary [6, 64, 65]. Therefore, an increase in dietary calcium, protein, sodium, or carbohydrate will increase calcium excretion as will a diet deficient in phosphorus [64, 65]. This is demonstrated in our patient who had a significant decrease in urinary calcium excretion following institution of the diet with restricted sodium, calcium, and protein (Table 2). It is important to note that with this dietary modification urinary PGE increased as urinary calcium fell, demonstrating that PGE was not the only variable affecting renal calcium excretion. Only when dietary considerations were removed by utilizing a fixed diet were we able to show the relationship between PGE and calcium excretion.

Not all patients with elevated PGE excretion have hypercalciuria. An example would be the typical patient with Bartter syndrome where levels of PGE are high and hypercalciuria is not a consistent finding [22, 26, 27, 66]. Similarly, dietary sodium restriction leads to a reduction in urinary calcium excretion but an elevation in urinary PGE excretion [49, 50]. Therefore, if PGE is a factor normally regulating urinary calcium excretion, it would appear to be interdependent with other factors.

The implications of this study as related to the large number of adult patients with idiopathic hypercalciuria is unclear. We suggest that PGE may have a role in some cases of idiopathic hypercalciuria, especially those associated with an apparent "renal leak." Further studies are needed in this population to address this question and to study the effects of prostaglandin inhibition.

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